PATENT COOPERATION TREATY

(8)

PCT

INTERNATIONAL PRELIMINARY REPORT ON PATENTABILITY

(Chapter II of the Patent Cooperation Treaty)

(PCT Article 36 and Rule 70)

Applicant's or agent's file reference 150388/KB	**FOR FURTHER ACTION**	See Form PCT/IPEA/416
International application No. PCT/CZ2004/000085	International filing date *(day/month/year)* 14.12.2004	Priority date *(day/month/year)* 16.12.2003
International Patent Classification (IPC) or national classification and IPC C07D491/22		
Applicant PLIVA-LACHEMA A.S. et al.		

1. This report is the international preliminary examination report, established by this International Preliminary Examining Authority under Article 35 and transmitted to the applicant according to Article 36.
2. This REPORT consists of a total of 5 sheets, including this cover sheet.
3. This report is also accompanied by ANNEXES, comprising:
   a. ☒ *sent to the applicant and to the International Bureau)* a total of 3 sheets, as follows:
      ☒ sheets of the description, claims and/or drawings which have been amended and are the basis of this report and/or sheets containing rectifications authorized by this Authority (see Rule 70.16 and Section 607 of the Administrative Instructions).
      ☐ sheets which supersede earlier sheets, but which this Authority considers contain an amendment that goes beyond the disclosure in the international application as filed, as indicated in item 4 of Box No. I and the Supplemental Box.
   b. ☐ *(sent to the International Bureau only)* a total of (indicate type and number of electronic carrier(s)) , containing a sequence listing and/or tables related thereto, in computer readable form only, as indicated in the Supplemental Box Relating to Sequence Listing (see Section 802 of the Administrative Instructions).

4. This report contains indications relating to the following items:

☒	Box No. I	Basis of the opinion
☐	Box No. II	Priority
☐	Box No. III	Non-establishment of opinion with regard to novelty, inventive step and industrial applicability
☐	Box No. IV	Lack of unity of invention
☒	Box No. V	Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement
☒	Box No. VI	Certain documents cited
☐	Box No. VII	Certain defects in the international application
☐	Box No. VIII	Certain observations on the international application

Date of submission of the demand	Date of completion of this report
09.07.2005	17.10.2005
Name and mailing address of the international preliminary examining authority: European Patent Office D-80298 Munich Tel. +49 89 2399 - 0 Tx: 523656 epmu d Fax: +49 89 2399 - 4465	Authorized Officer Härtinger, S Telephone No. +49 89 2399-8289

INTERNATIONAL PRELIMINARY REPORT ON PATENTABILITY

International application No.
PCT/CZ2004/000085

Box No. I Basis of the report

1. With regard to the **language**, this report is based on the international application in the language in which it was filed, unless otherwise indicated under this item.

   ☐ This report is based on translations from the original language into the following language , which is the language of a translation furnished for the purposes of:

   ☐ international search (under Rules 12.3 and 23.1(b))
   ☐ publication of the international application (under Rule 12.4)
   ☐ international preliminary examination (under Rules 55.2 and/or 55.3)

2. With regard to the **elements*** of the international application, this report is based on *(replacement sheets which have been furnished to the receiving Office in response to an invitation under Article 14 are referred to in this report as "originally filed" and are not annexed to this report)*:

   Description, Pages

   1-6 as originally filed

   Claims, Numbers

   1-13 received on 09.07.2005 with letter of 15.06.2005

   ☐ a sequence listing and/or any related table(s) - see Supplemental Box Relating to Sequence Listing

3. ☐ The amendments have resulted in the cancellation of:

   ☐ the description, pages
   ☐ the claims, Nos.
   ☐ the drawings, sheets/figs
   ☐ the sequence listing *(specify)*:
   ☐ any table(s) related to sequence listing *(specify)*:

4. ☐ This report has been established as if (some of) the amendments annexed to this report and listed below had not been made, since they have been considered to go beyond the disclosure as filed, as indicated in the Supplemental Box (Rule 70.2(c)).

   ☐ the description, pages
   ☐ the claims, Nos.
   ☐ the drawings, sheets/figs
   ☐ the sequence listing *(specify)*:
   ☐ any table(s) related to sequence listing *(specify)*:

* *If item 4 applies, some or all of these sheets may be marked "superseded."*

INTERNATIONAL PRELIMINARY REPORT ON PATENTABILITY

International application No.
PCT/CZ2004/000085

Box No. V Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement

1. Statement

Novelty (N)	Yes:	Claims	1-13
	No:	Claims	
Inventive step (IS)	Yes:	Claims	1-13
	No:	Claims	
Industrial applicability (IA)	Yes:	Claims	1-13
	No:	Claims	

2. Citations and explanations (Rule 70.7):

see separate sheet

Box No. VI Certain documents cited

1. Certain published documents (Rule 70.10)

and / or

2. Non-written disclosures (Rule 70.9)

see separate sheet

Section V:

1. The application relates to a process for the preparation of 7-ethyl-10-hydroxycamptothecin. The process makes use of the ring A activation by providing a hydrogenated pyridine ring B and subsequent oxidation.

   The relevant prior art has been indicated in the search report.

   D1: WOOD J L ET AL: "An Efficient Conversion of Camtothecin to 10-Hydroxycamptothecin" J. ORG. CHEM., vol. 60, 1995, pages 5739-5740, XP002323603 ISSN: 0022-3263
   D2: US-A-4 473 692 (MIYASAKA ET AL) 25 September 1984 (1984-09-25)
   D3: US-A-5 734 056 (BURK ET AL) 31 March 1998 (1998-03-31)

2. The processes disclosed in D1, D2 and D3 are analogous to the presently claimed synthesis method and differ merely in the absence of the alkyl group at position 7. Hence, the claimed subject-matter appears to be novel in the sense of Art. 33(2) PCT.

3. D1 is considered to be the closest prior art. It teaches (cf. page 5739, right hand side and page 5740) the general synthesis strategy for 10-hydroxy substituted camptothecin derivatives by activating this position first through the reduction of the pyridine ring B, and then by oxidizing rings A and B. On the pending paragraph between the pages 5739 and 5740, it is taught, that only particular oxidant-solvent combination are technically useful, as a series of alternative oxidants, either lacked regioselectivity to the ring position 10, or further oxidised the desired end product. "The key turned out to be conducting the oxidation in a solvent mixture consisting of water and a miscible organic solvent. Among several systems that gave good results, 1:1 acetic acid/water provided the highest yield and selectivity ... With iodobenzene diacetate as the oxidant, 2 was typically isolated in 88-91% yield". D2 uses also the activation strategy taught by D1, namely the reduction of the pyridine B ring with subsequent introduction of substituents at the 10 position in ring A (cf. column 9). The skilled person will notice, that the presence or absence of a substituent at position 7 in the pyridine ring, is of no relevance for this synthesis strategy. By consequence,

the skilled person, who was looking to solve the problem of providing an alternative method for the production 7-ethyl-10-hydroxycamptothecin, would have use the method of D1 in plain analogy with a reasonable expectation of success.

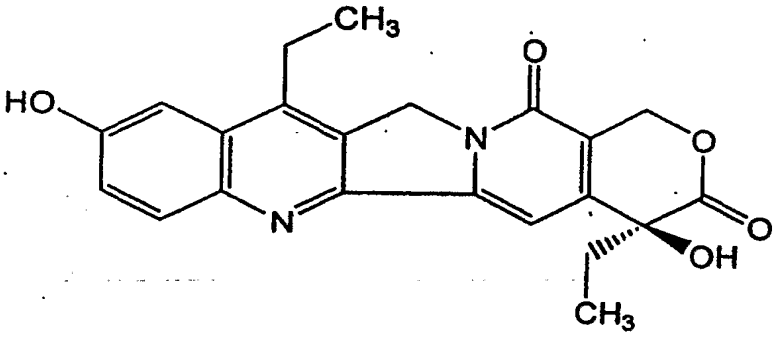
However, applicants have shown in their letter dated 15.06.05 by way of a comparative test, that the combination of process features as stated in amended claim 1, in particular the ranges given for the reaction temperature and reaction time, is linked with a technical effect, which cannot be derived from the closest prior art. In comparison to the process disclosed in D1, a higher yield could be obtained in a shorter reaction time, whereby the purity of the product is also increased. Since the prior art does not give a hint, which process parameters must be modified in order to obtain these beneficial properties, and the comparative test show that the presently chosen parameter values for the process features are not foreshadowed by D1, the said process features are considered to contribute in a not obvious manner to the solution of the problem of providing an improved method for synthesizing hydroxycamptothecin derivatives. Hence, the presently suggested use of the iodobenzene diacetate/water/acetic acid system under the specified conditions of claim 1 appears therefore to meet the requirement of Art. 33(3) PCT.

Section VI:

1. The international application D4 (= WO 2004/100897 A, SCINOPHARM TAIWAN, LTD, 25 November 2004) discloses an analogous process, which at least shares many of the present process features. As D4 has been published between the priority and filing date of the present application, this document does not form part of the state of the art as defined by the PCT. By consequence, D4 has been disregarded from further consideration.

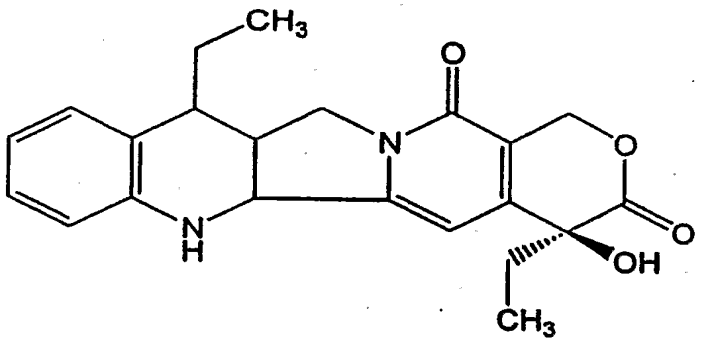
C L A I M S

1. The method of manufacturing of 7-ethyl-10-hydroxy-camptothecin of formula I



(I)

characterized in that 7-ethyl-1,2,6,7-tetrahydrocamptothecin of formula IV

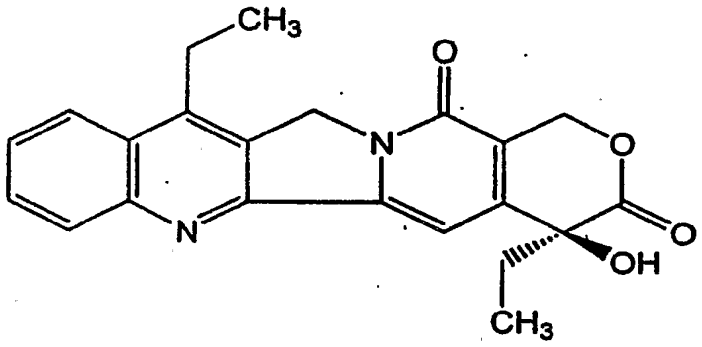


(IV)

is oxidized with iodobenzene diacetate in acetic acid and in the presence of water under the conditions consisting in that iodobenzene diacetate is used in an amount of 0.99 to 1.85 mol per 1 mol of 7-ethyl-1,2,6,7-tetrahydrocamptothecin, acetic acid is used in an amount of 668 to 1001 mol per 1 mol of 7-ethyl-1,2,6,7-tetrahydrocamptothecin, water is used in an amount of 980 to 1880 mol per 1 mol of 7-ethyl-1,2,6,7-tetrahydrocamptothecin and the oxidation is carried out at a temperature from 15 to 30 °C for 5 to 30 minutes.

SUBSTITUTE SHEET

2. The method according to claim 1, **characterized in that** the starting 7-ethyl-1,2,6,7-tetrahydrocamptothecin is obtained by hydrogenation of 7-ethylcamptothecin of formula II



(II)

in a saturated aliphatic monocarboxylic acid having 1 to 3 carbon atoms, using hydrogen in the presence of a hydrogenation catalyst and a sulfur compound that partly deactivates the hydrogenation catalyst.

3. The method according to claim 2, **characterized in that** the saturated aliphatic acid is formic acid, acetic acid or trifluoroacetic acid.

4. The method according to claim 3, **characterized in that** acetic acid is used in an amount of 791 to 1187 mol, preferably 890 to 1088 ml, per 1 mol of 7-ethylcamptothecin.

5. The method according to claim 2, **characterized in that** the sulfur compound that partly deactivates the hydrogenation catalyst is dimethyl sulfoxide.

6. The method according to claim 5, **characterized in that** dimethyl sulfoxide is used in an amount of 0,18 to 0,33, preferably 0,23 to 0,28 ml, per 1 mol of 7-ethylcamptothecin.

7. The method according to claim 2, **characterized in that** the hydrogenation catalyst is a noble metal.

8. The method according to claim 7 **characterized in that** the noble metal is platinum.

9. The method according to claim 8, **characterized in that** platinum is used on an activated carbon or aluminium oxide carrier.

10. The method according to claim 9, **characterized in that** platinum is used in an amount of 0,018 to 0,027 mol, preferably 0,020 to 0,025 mol, per 1 mol of 7-ethylcamptothecin, in form of a hydrogenation catalyst, formed by platinum on an activated carbon with platinum content 5 %.

11. The method according to claim 2 **characterized in that** the hydrogenation is carried out at a pressure from 0,3 to 0,7 MPa, preferably at a pressure from 0,4 to 0,6 MPa.

12. The method according to claim 11, **characterized in that** the hydrogenation is carried out at a temperature from 45 to 85 °C, preferably at 58 to 72 °C.

13. The method according to claim 11, **characterized in that** the hydrogenation is carried out for 24 to 70 hours, preferably for 40 to 50 hours.